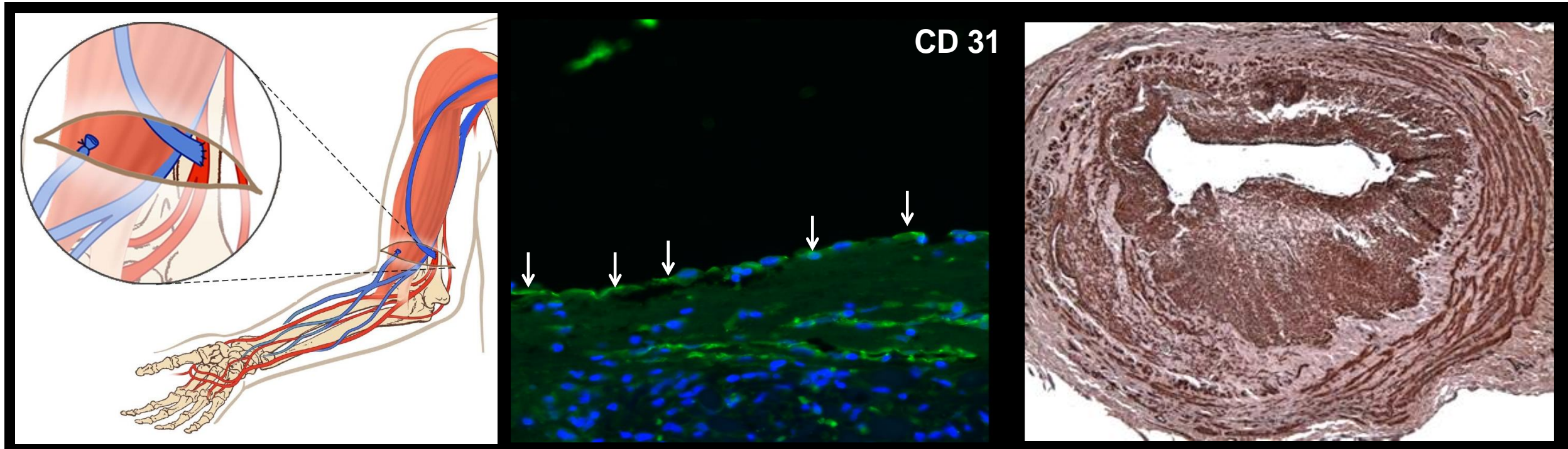


# Novel Experimental and Clinical Therapies: *of Pigs,* *Patients and Policy!!*

**Prabir Roy-Chaudhury MD, PhD, FACP, FRCP (Edin)**  
**University of Arizona and SAVAHCS**



# Disclosures

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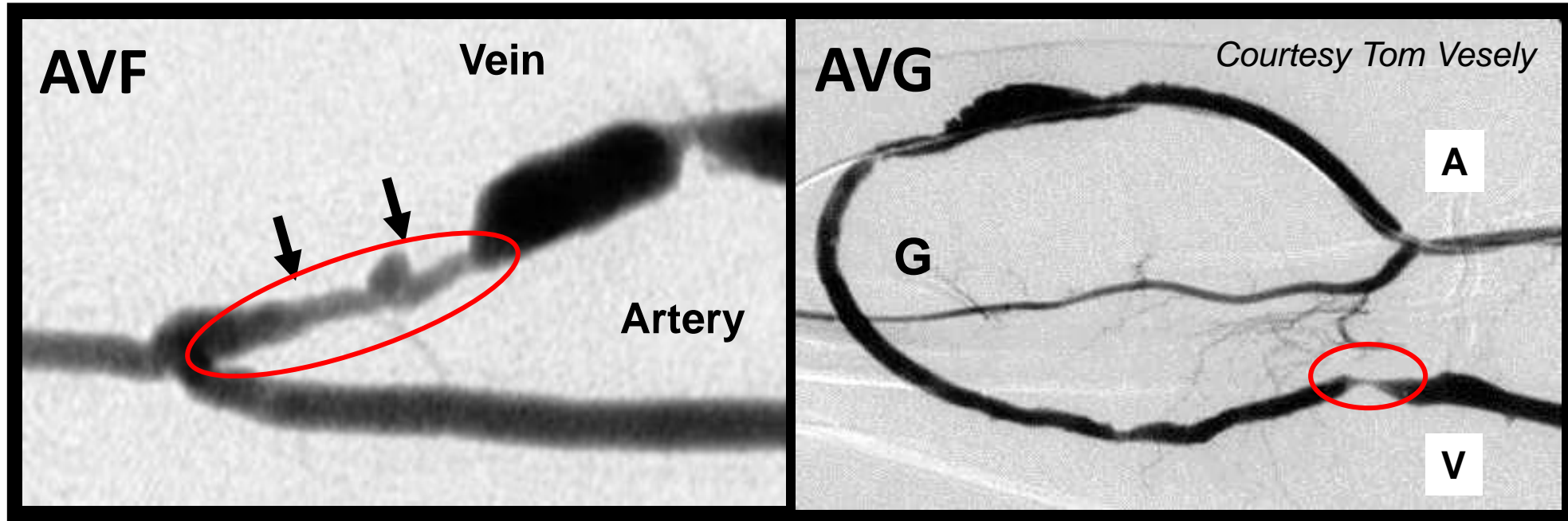
- **Founder and Chief Scientific Officer of Inovasc**
- **Consultant/Advisory Board: WL Gore, Medtronic, Bard, Cormedix, TVA, Humacyte, Akebia, Relypsa, Vascular Therapies**

# Outline

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- Pathology and pathogenesis of dialysis vascular access dysfunction with a focus on AVF maturation failure
- Novel biotechnology and bioengineering solutions for dialysis vascular access dysfunction
- Policy and process of care pathways to improve dialysis vascular access care (**AVF maturation**)
- Messages for the future!!

# Radiological presentation of dialysis vascular access dysfunction

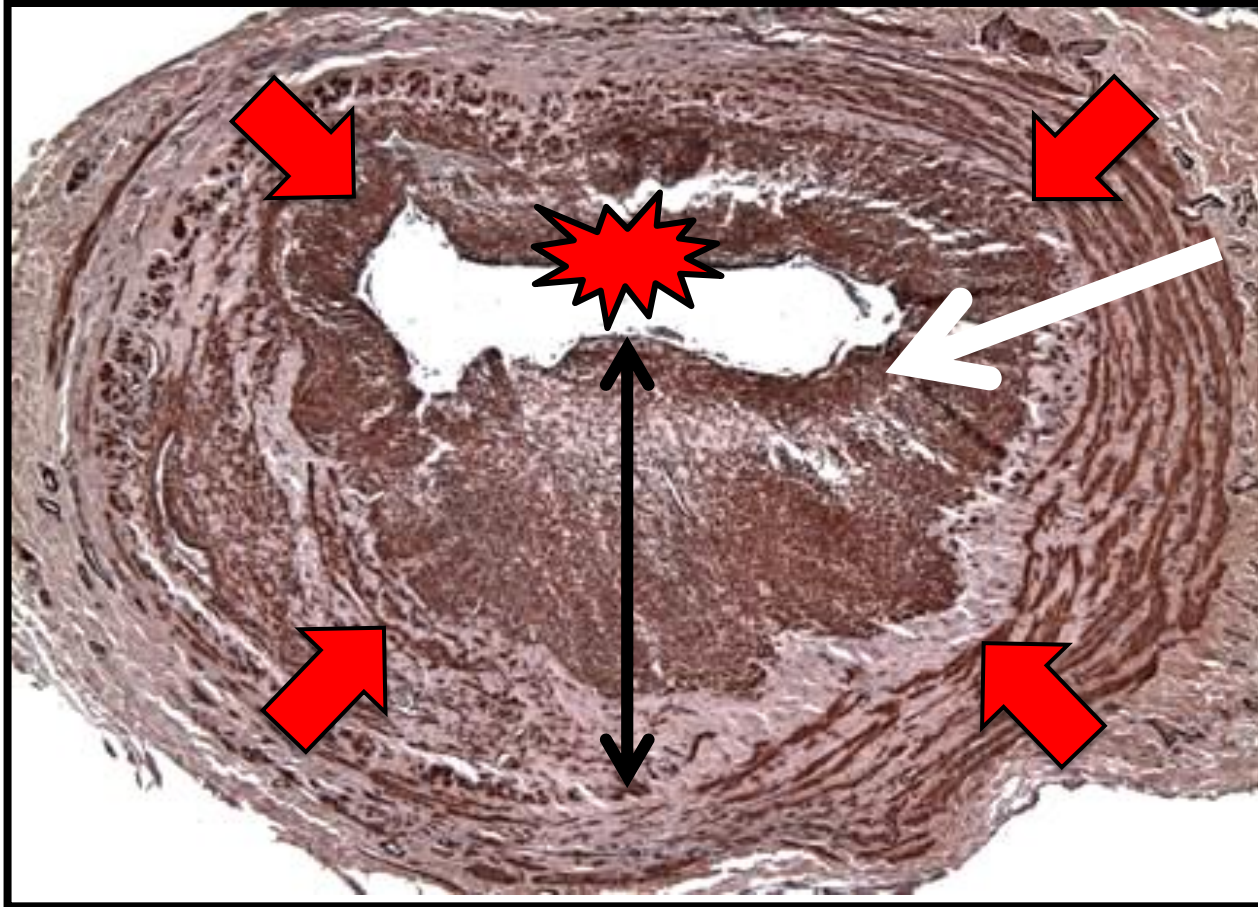


- Perianastomotic stenosis
- AVF non maturation

- Stenosis at the graft-vein anastomosis
- Graft thrombosis

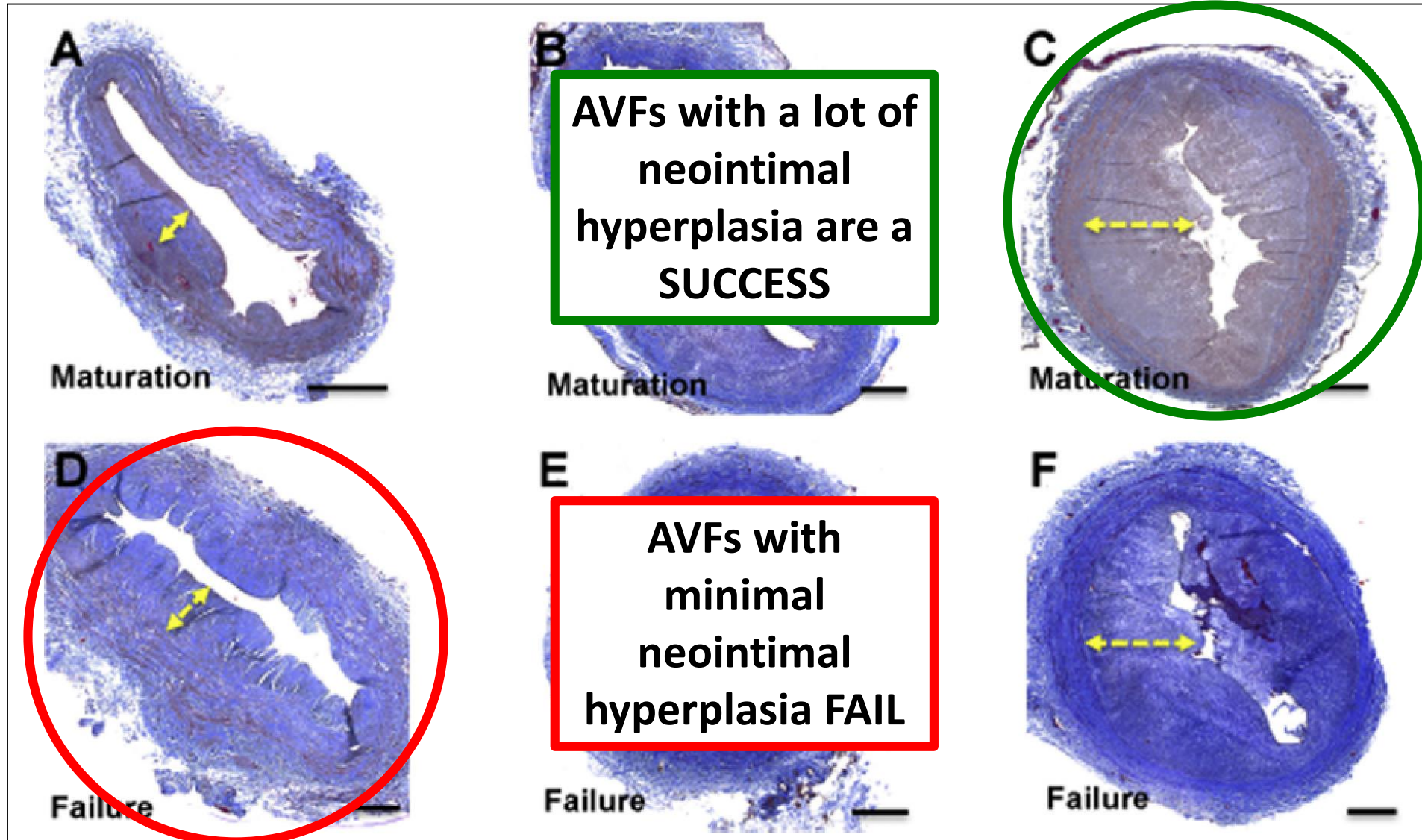


# Histological presentation of AVF maturation failure



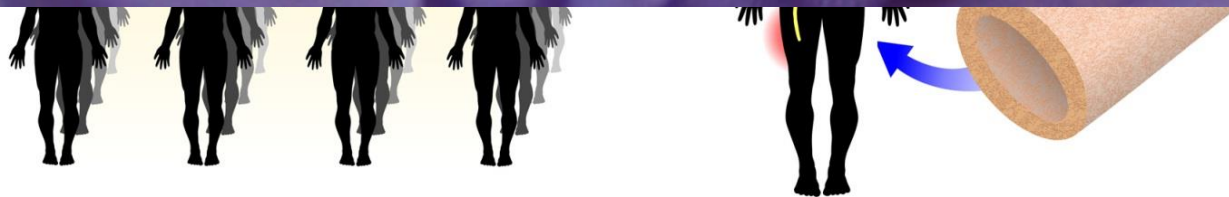
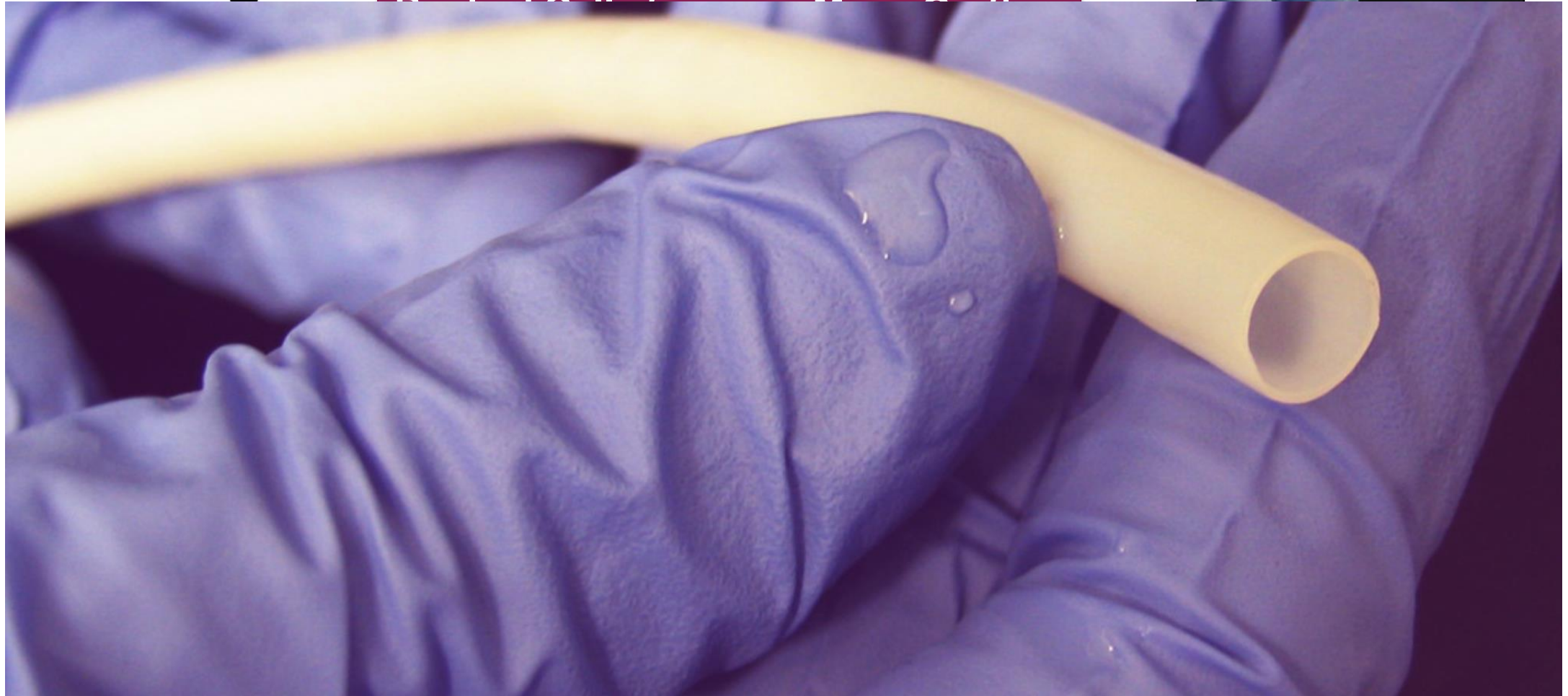
- Aggressive venous neointimal hyperplasia
- Smooth muscle cells and myofibroblasts that migrate in from the media and perhaps the adventitia as a result of vascular (**hemodynamic**) injury
- Inward remodeling or at least a lack of outward remodeling
- **Both the NH and inward remodeling made worse by the inflammation, oxidative stress and endothelial dysfunction that is present in our CKD/ESRD patients**

# Negative remodeling may be more important than neointimal hyperplasia



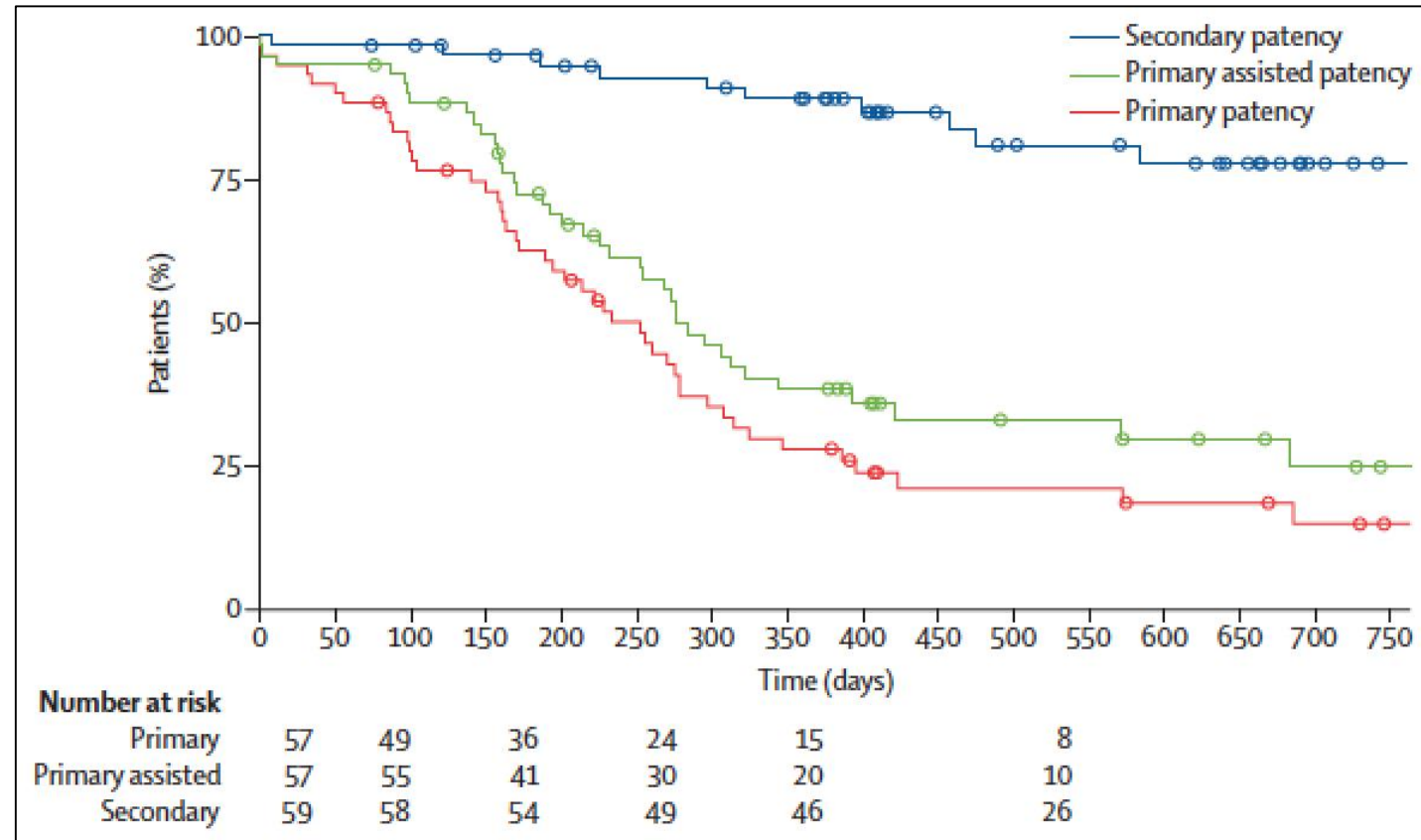
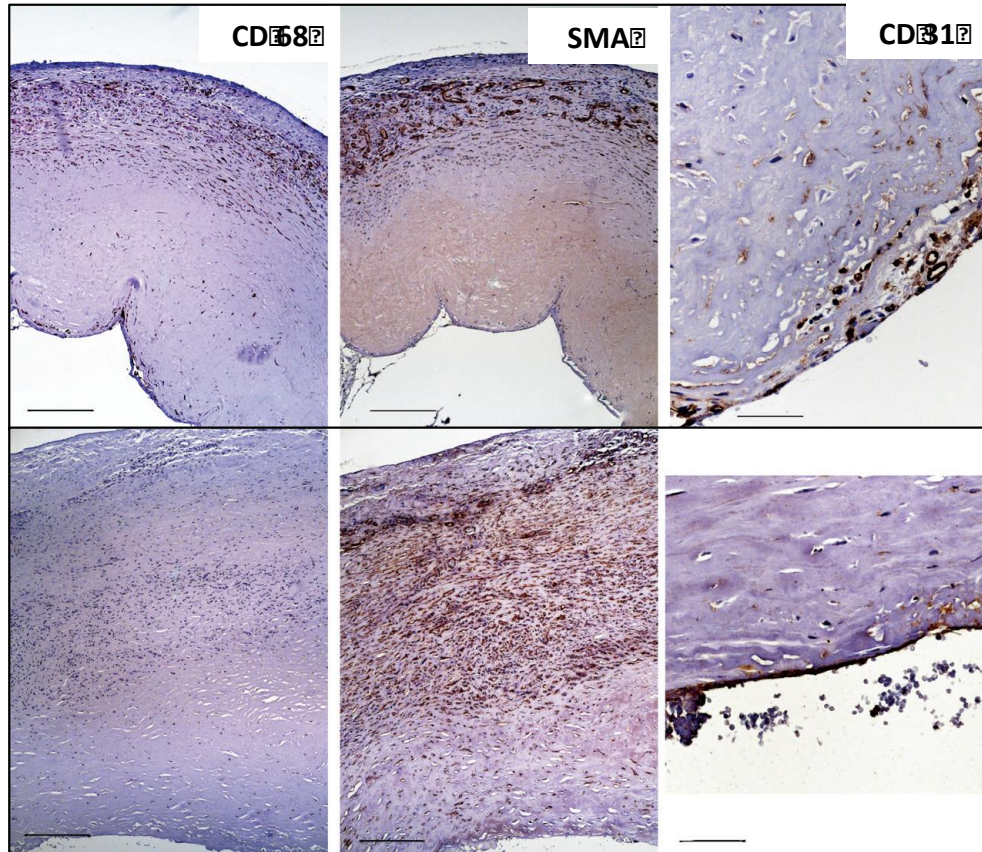


# Tissue Engineered Grafts for Vascular Access



# Tissue Engineered Grafts for Vascular Access

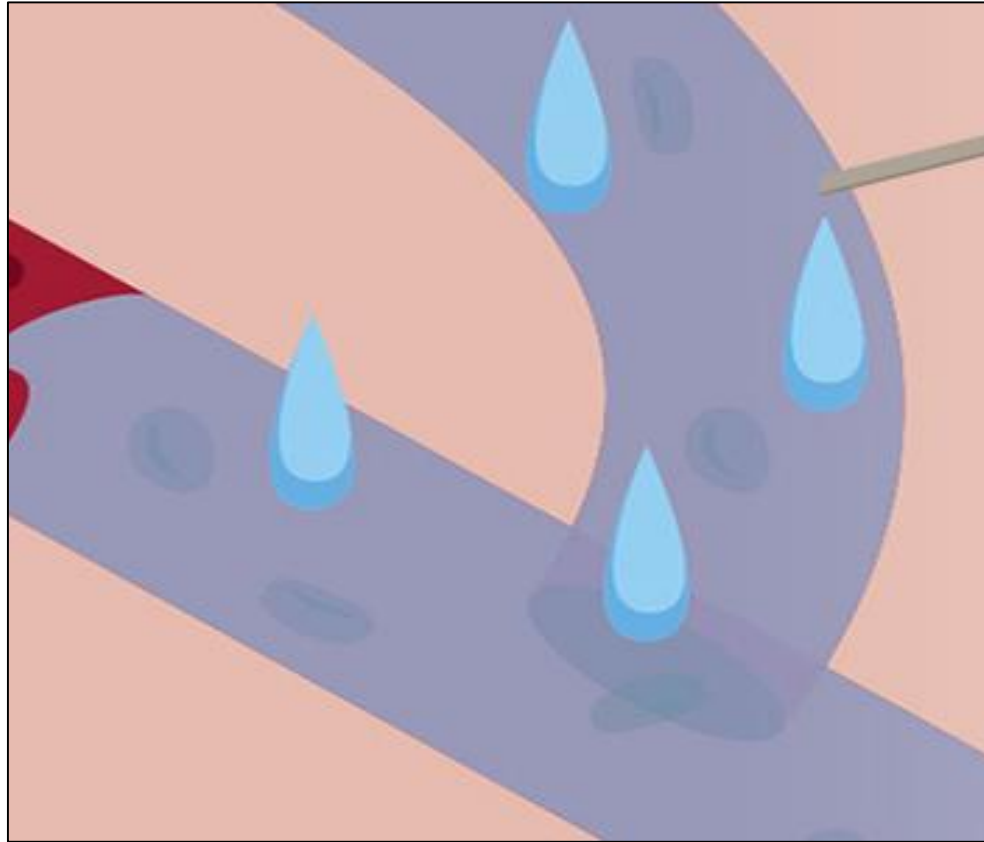
16 weeks



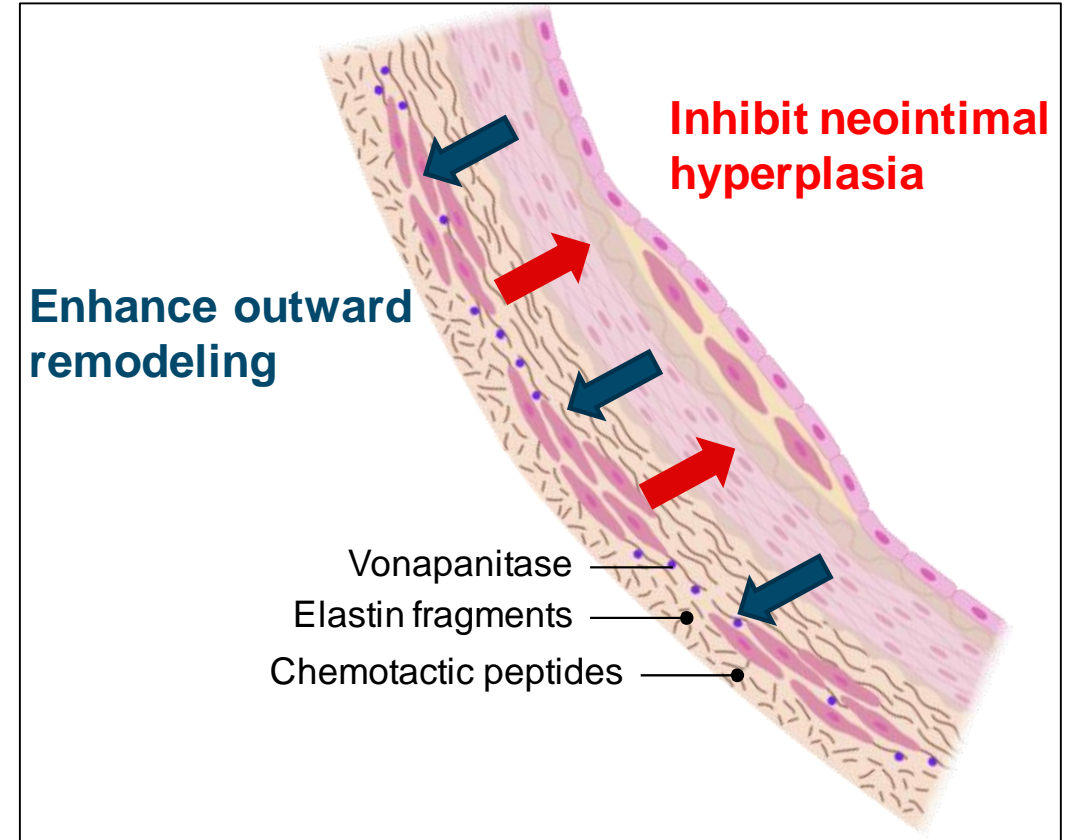
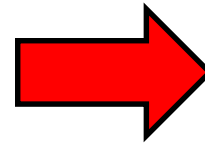
**Results of the Phase III HUMANITY trial are pending**



# Vonapanitase: a recombinant elastase for AVF maturation

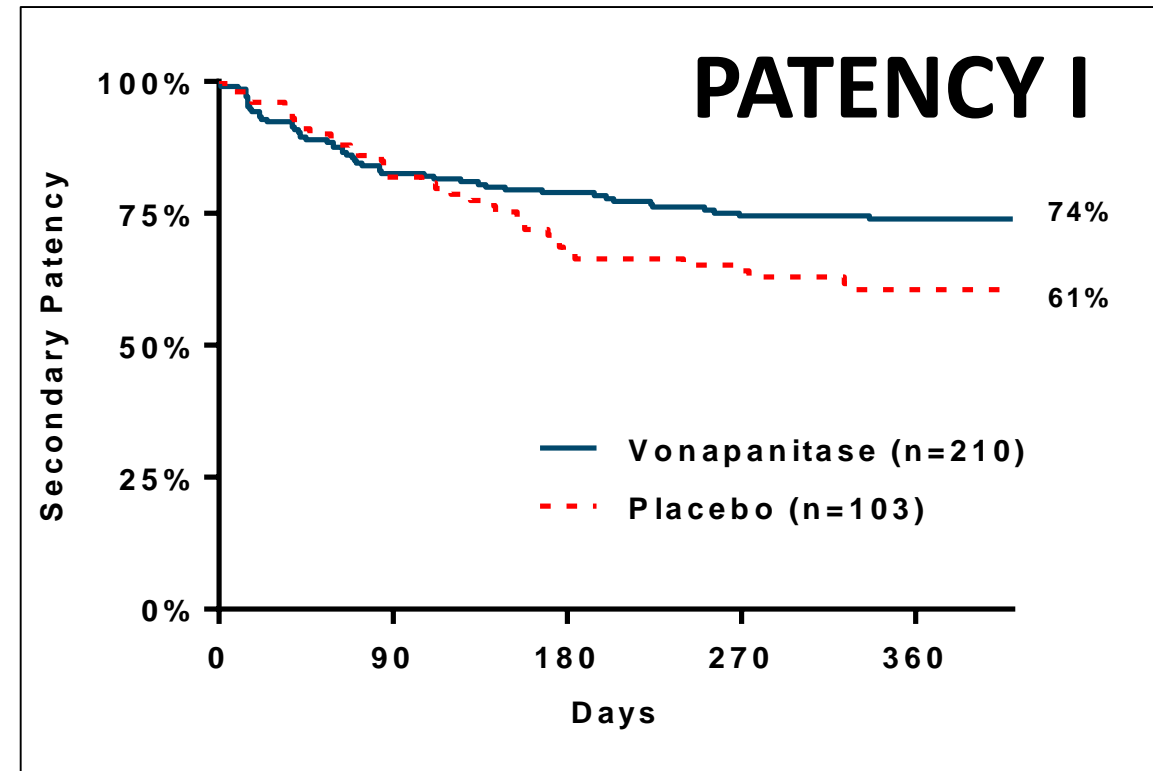
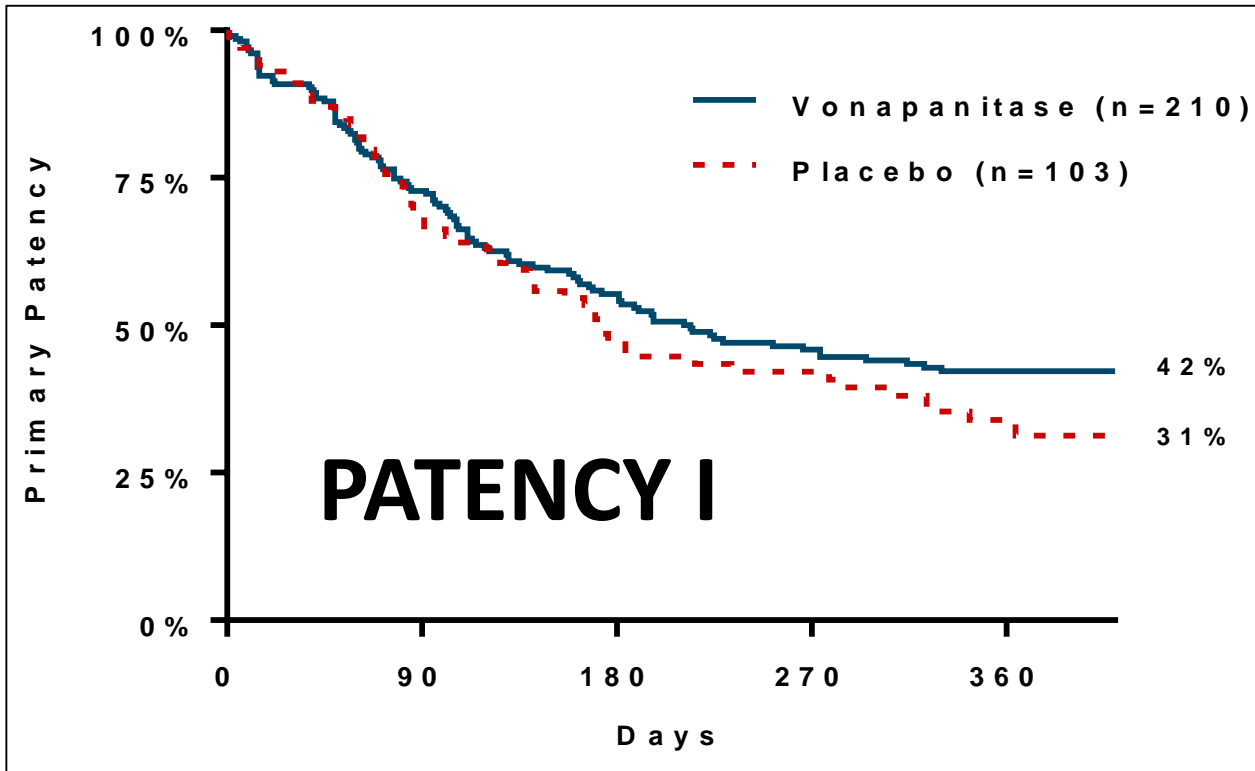


**Elastase**



**Elastin fragments**

# Vonapanitase: a recombinant elastase for AVF maturation



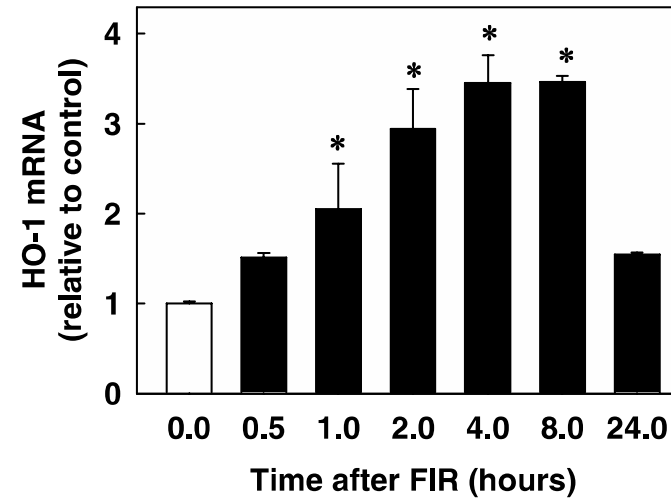
**No difference in primary end point of unassisted primary patency**

**Significant improvement in secondary patency**

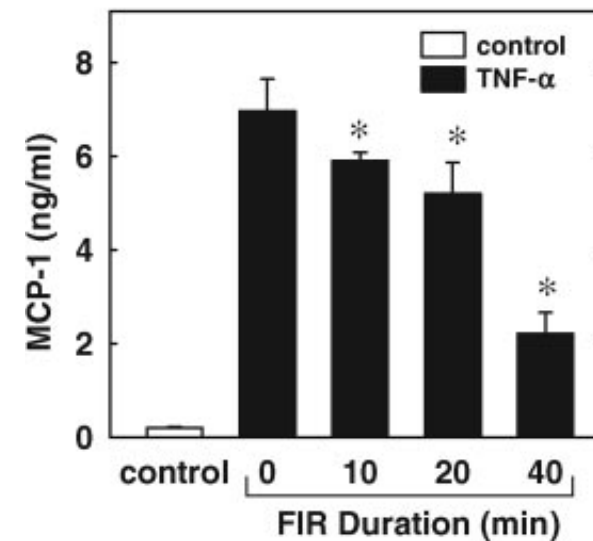
# Far Infra Red Therapy (Rationale)



- **Increases HO-1 and reduces oxidative stress**

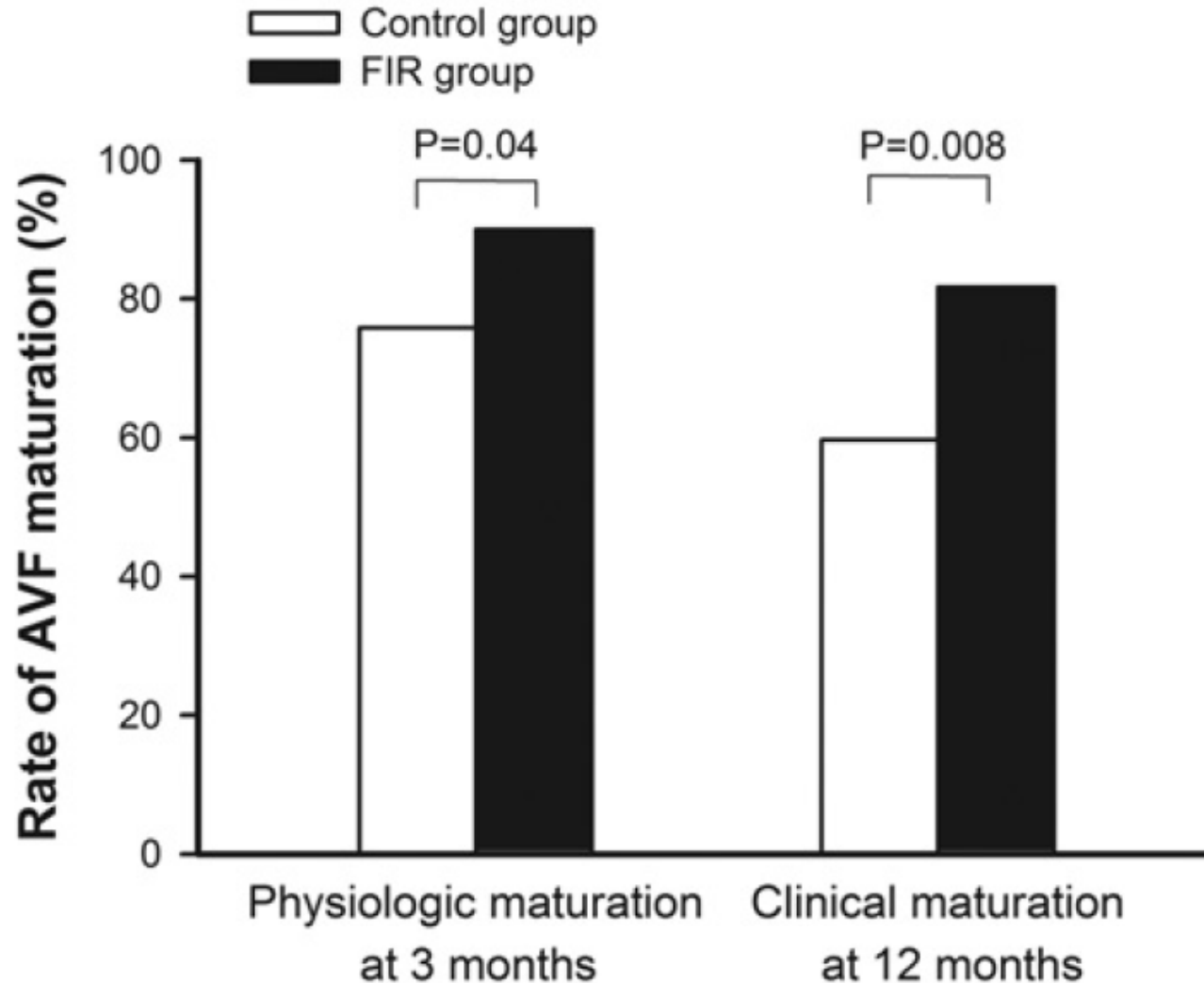


- **Decreases inflammation by reducing MCP-1**





# Far Infra Red Therapy improves AVF maturation

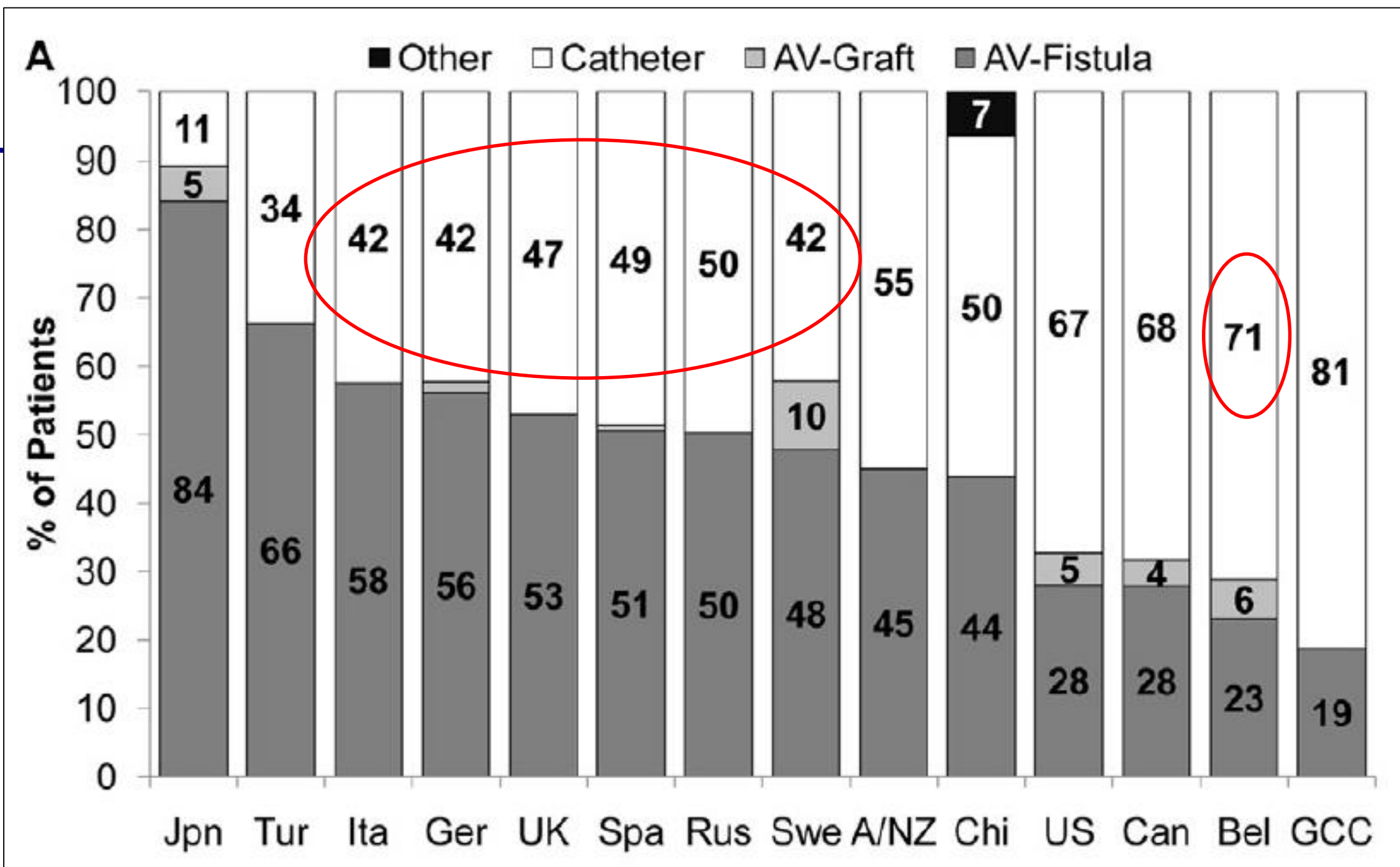


- **22% increase in clinical maturation at 12 months!**

# Far Infra Red Therapy in use!

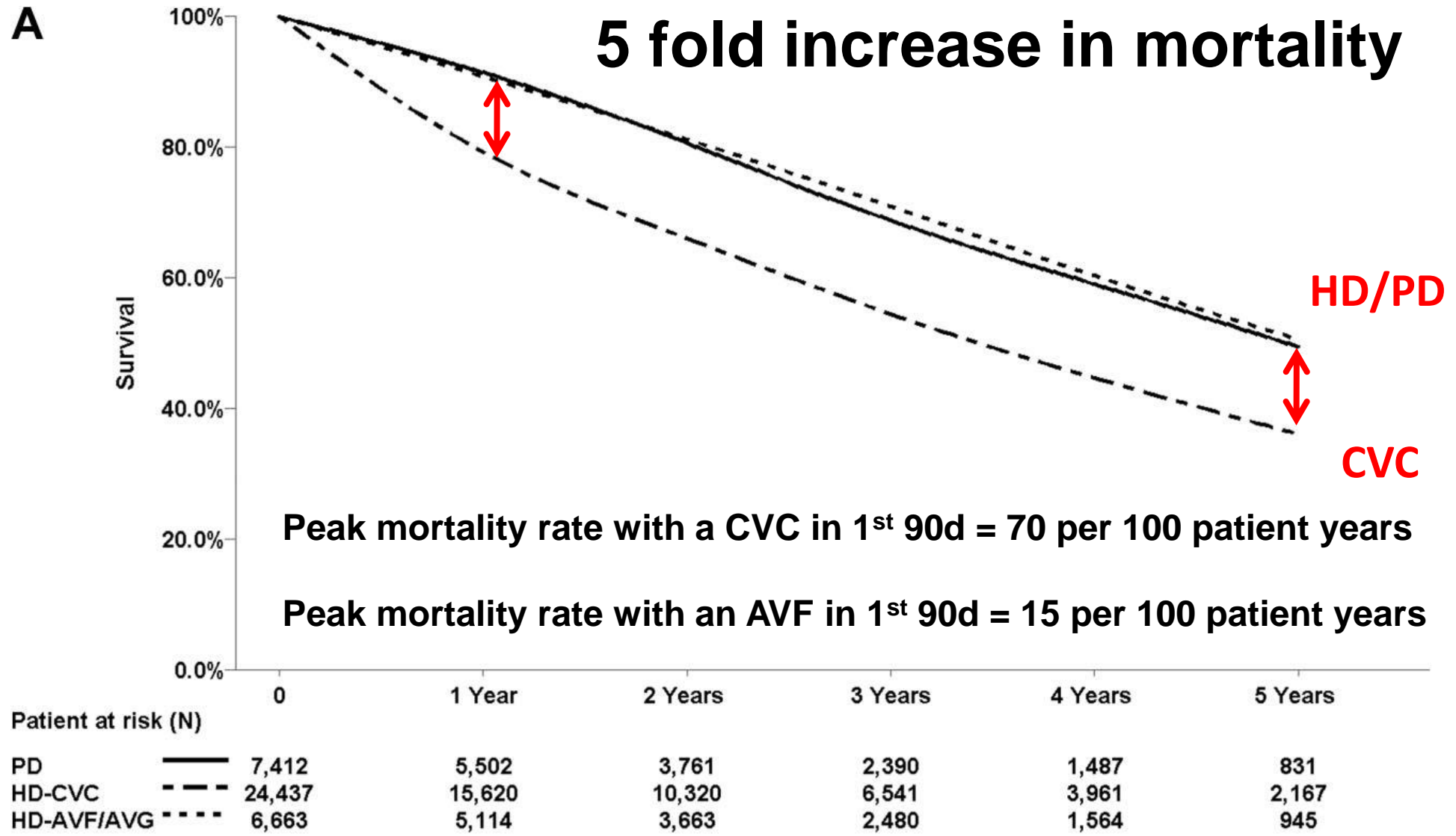
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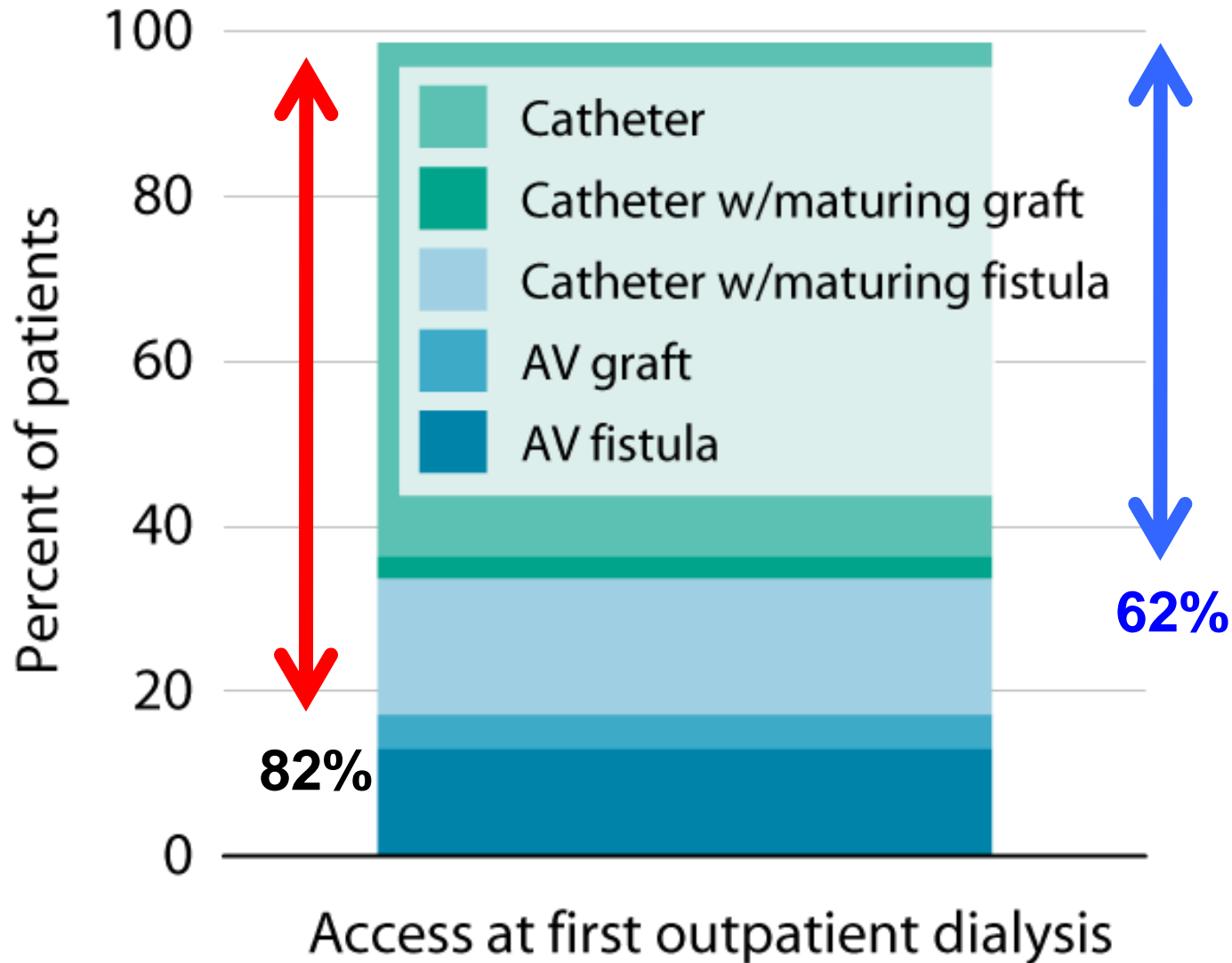




# Catheters kill patients!

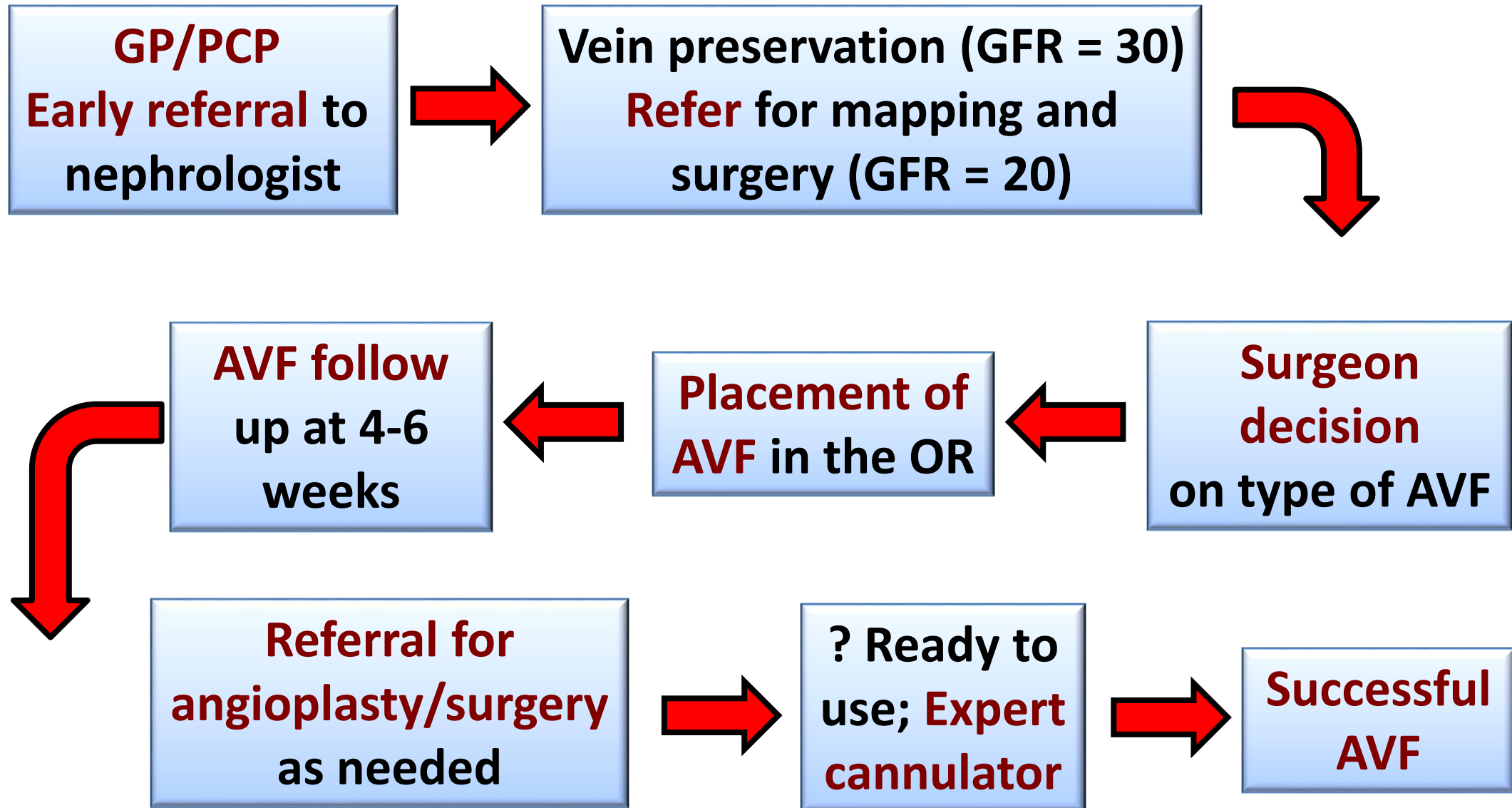


# The “Achilles Heel”: 60-80% of incident hemodialysis patients start dialysis with a catheter!



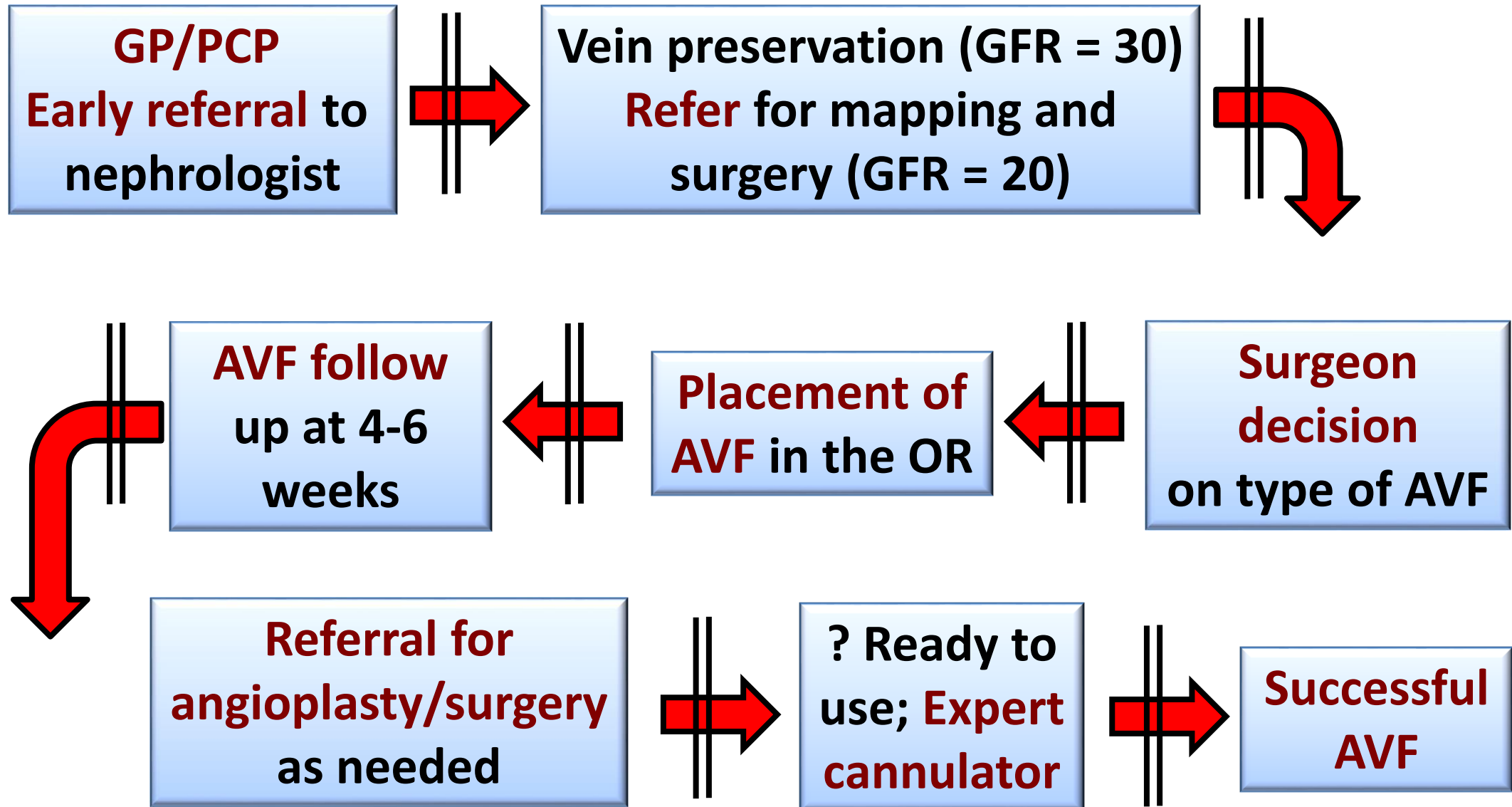
- 5 fold greater mortality in first 90 days on HD
- **Disgraceful!!**
- **Not a failure of technology or biology**
- **Dismal failure of communication and logistics!!**
- **Process of Care**

# Huge reduction in morbidity and mortality if every patient starting hemodialysis had a functional AVF



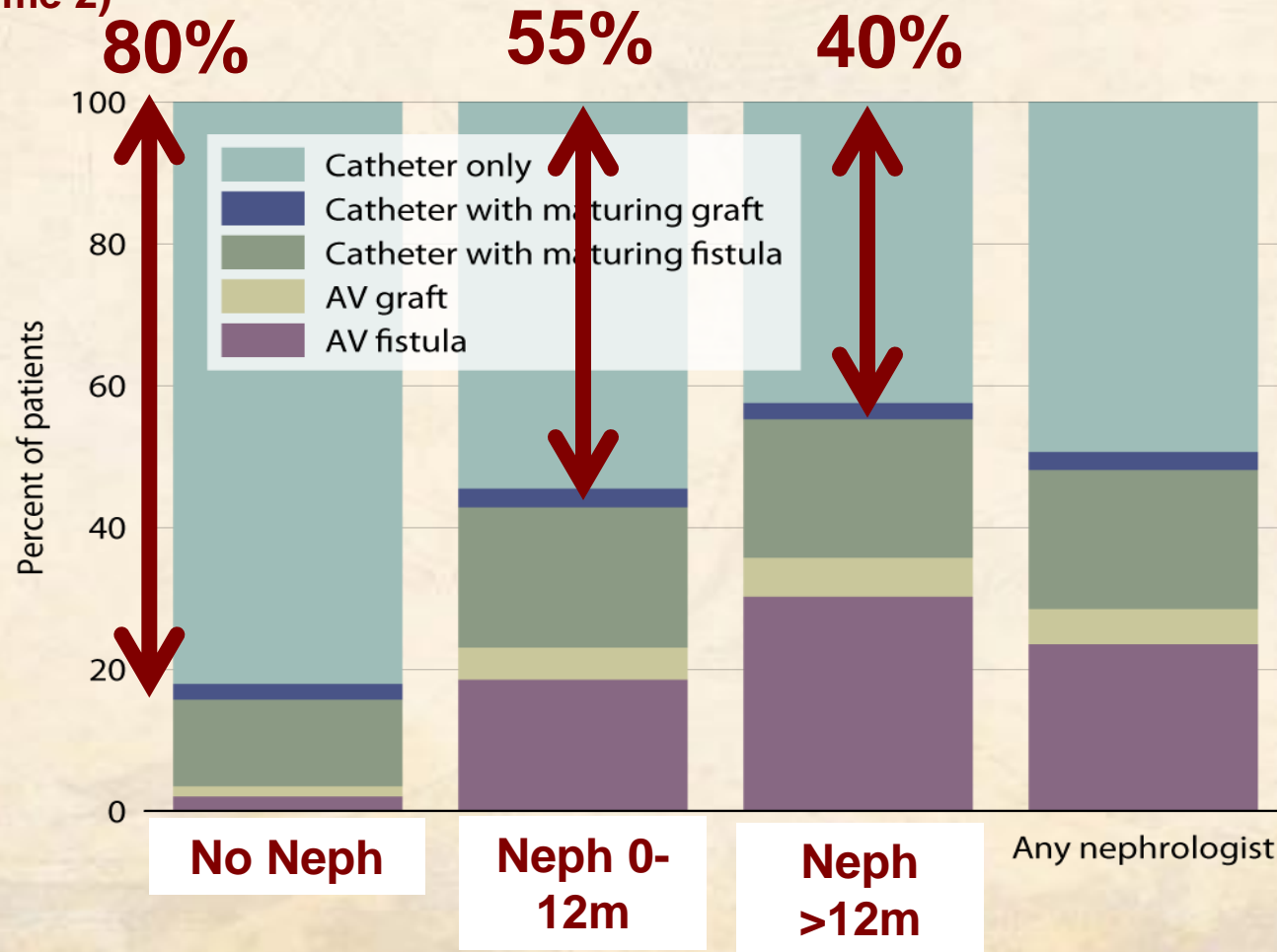


# Process of Care barriers at each of these steps



# Access use at first outpatient dialysis, by pre-ESRD nephrology care, 2008

Figure 3.1 (Volume 2)



Incident hemodialysis patients, 2008.

# Why 40% catheter starts even if seen by a nephrologist for > 12 months?

## Lopez-Varga et al. Am J Kidney Dis 2011

### Barriers to Timely Arteriovenous Fistula Creation: A Study of Providers and Patients

*Pamela A. Lopez-Vargas, MPH,<sup>1</sup> Jonathan C. Craig, FRACP, MMed, PhD,<sup>1,2</sup>  
Martin P. Gallagher, FRACP, MPH, PhD,<sup>3</sup> Rowan G. Walker, FRACP, MD,<sup>4</sup>  
Paul L. Snelling, FRACP,<sup>5</sup> Eugenia Pedagogos, FRACP, PhD,<sup>4</sup>  
Nicholas A. Gray, FRACP,<sup>6</sup> Murthy D. Divi, FRACP,<sup>7</sup>  
Alastair H. Gillies, MRACP, FRACP, PhD,<sup>8</sup> Michael G. Suranyi, FRACP, PhD,<sup>9</sup>  
Hla Thein, FRACP,<sup>10</sup> Stephen P. McDonald, FRACP, PhD,<sup>11,12</sup>  
Christine Russell, BA, FRACS,<sup>12</sup> and  
Kevan R. Polkinghorne, FRACP, MClInEpi, PhD<sup>13,14</sup>*

AJKD

## Lee, Roy-Chaudhury, Thakar Am J Kidney Dis 2011

Editorial

### Improving Incident Fistula Rates: A Process of Care Issue

Related Article, p. 873

ary outcomes included physician, patient, and organizational barriers responsible for delays in achieving a

**Battle for dialysis vascular access will be won or lost in the CKD stage**

- Late referral by nephrologists to surgeons
- Unpredictability of when patients will start HD
- Non-acceptance of the need for HD
- Need for more resources (specifically access coordinators) so that we can develop coordinated, integrated access care programs in the CKD phase

# Surgery

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- **Good surgeon**
- **Full range of vascular access procedures (from difficult catheters to transpositions to grafts)**



# Good Surgeon

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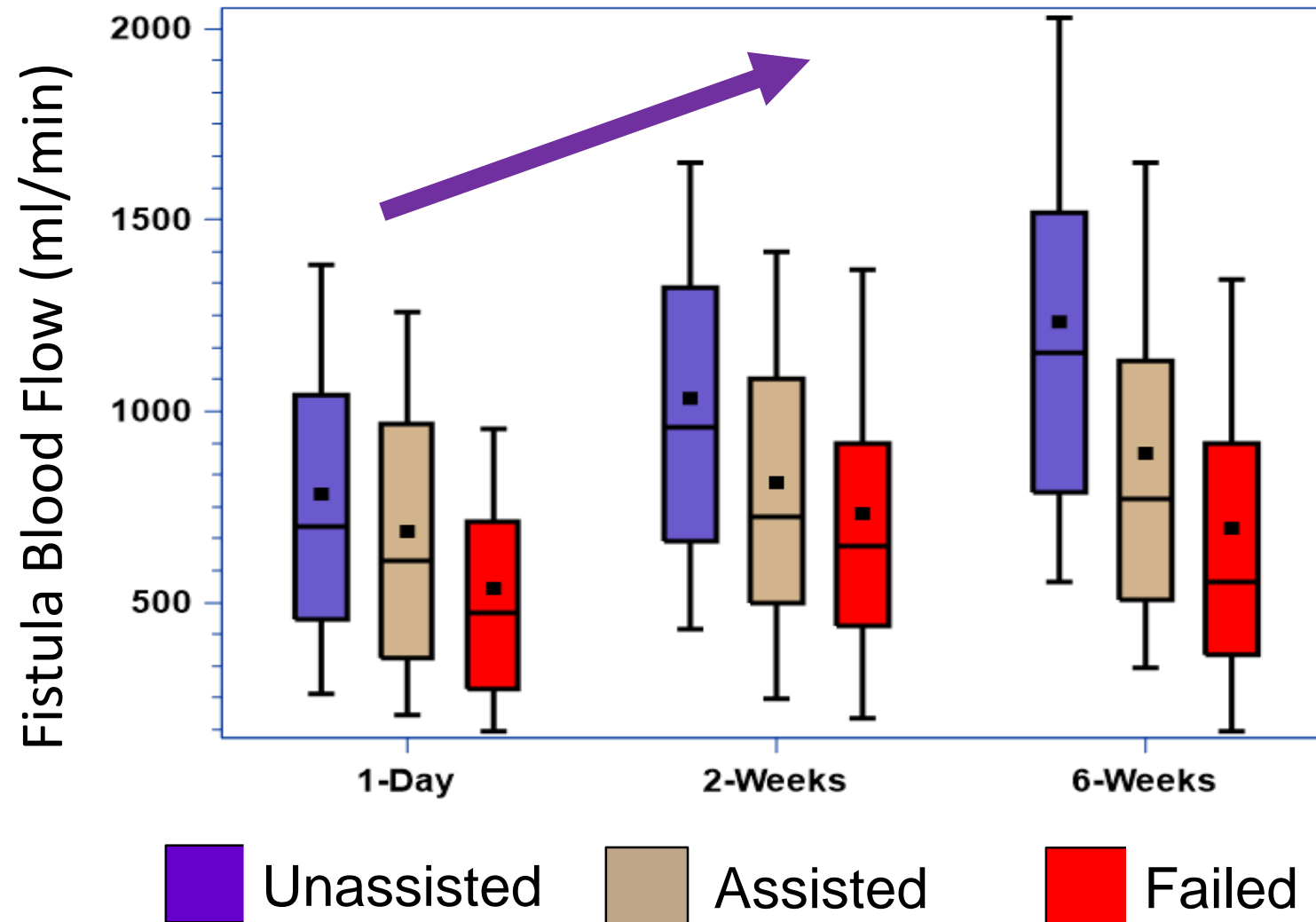
- Interested, dedicated and committed
- Wisdom to make a judgement call about being able to place **the right access in the right patient at the right time**
- We need **“judgement calls”** because we don't have adequate predictive data

# **Hemodialysis Fistula Maturation Consortium: *Can we predict whose AVF will fail?***

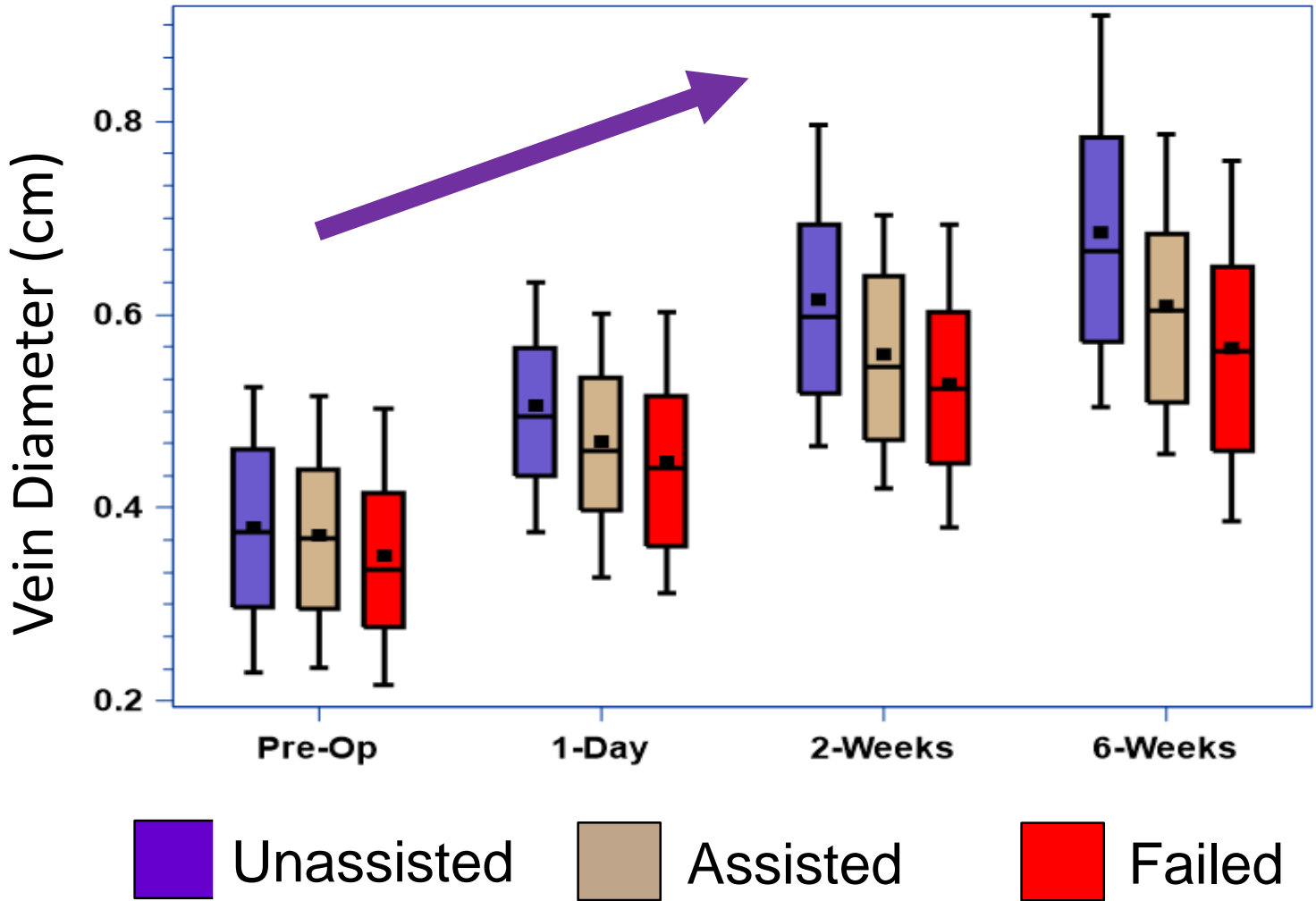
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- **NIH funded prospective observational cohort study**
- **7 centers; 602 participants**
- **Single stage AVF creation**
- **Pre-operative, intra-operative and post-operative data collection**
- **AVFs followed up till abandonment**

# Vascular anatomy and blood flow (FLOW)

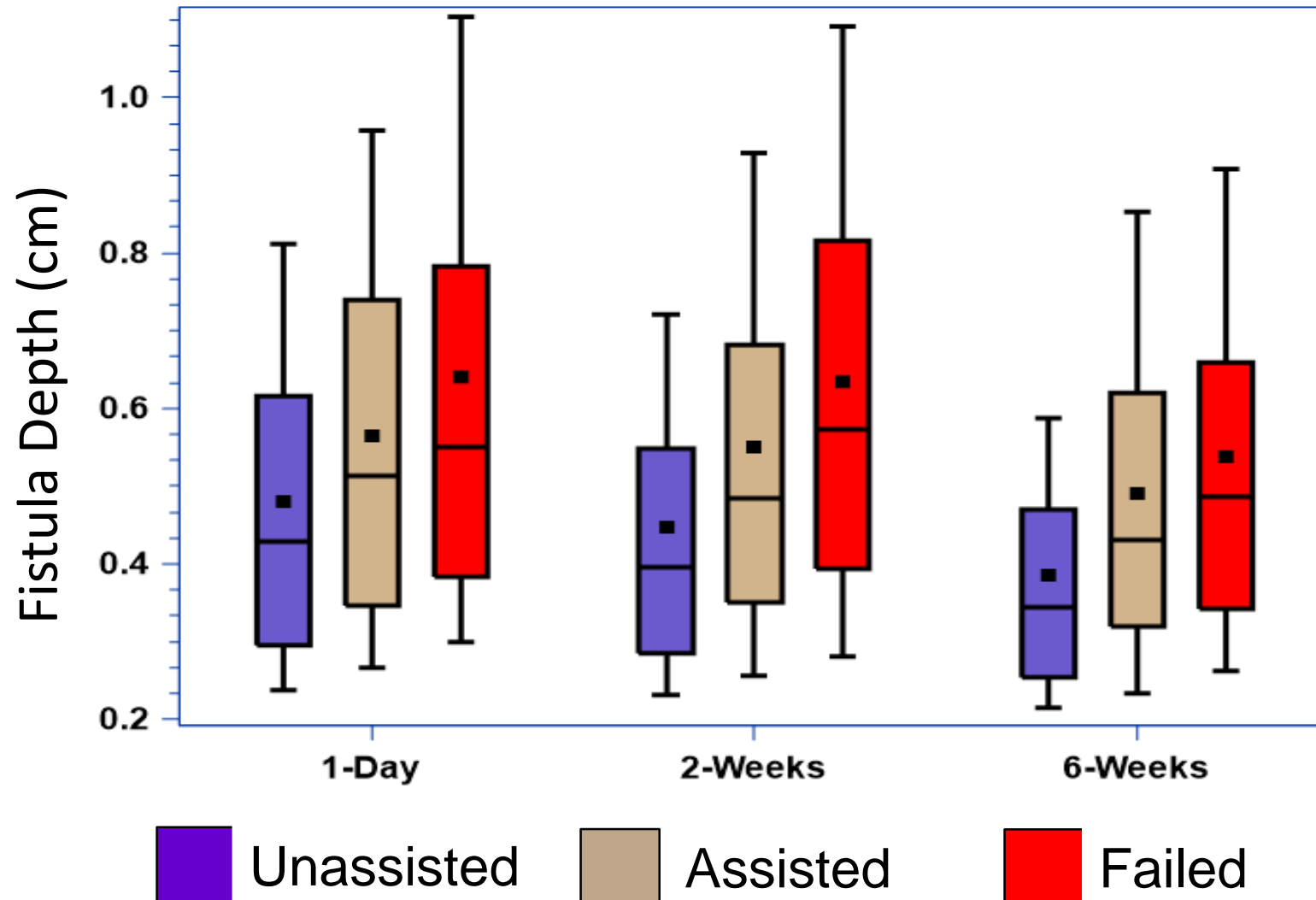


# Vascular anatomy and blood flow (DIAMETER)





# Vascular anatomy and blood flow (DEPTH)



# Technology can Change Existing Clinical Paradigms!!

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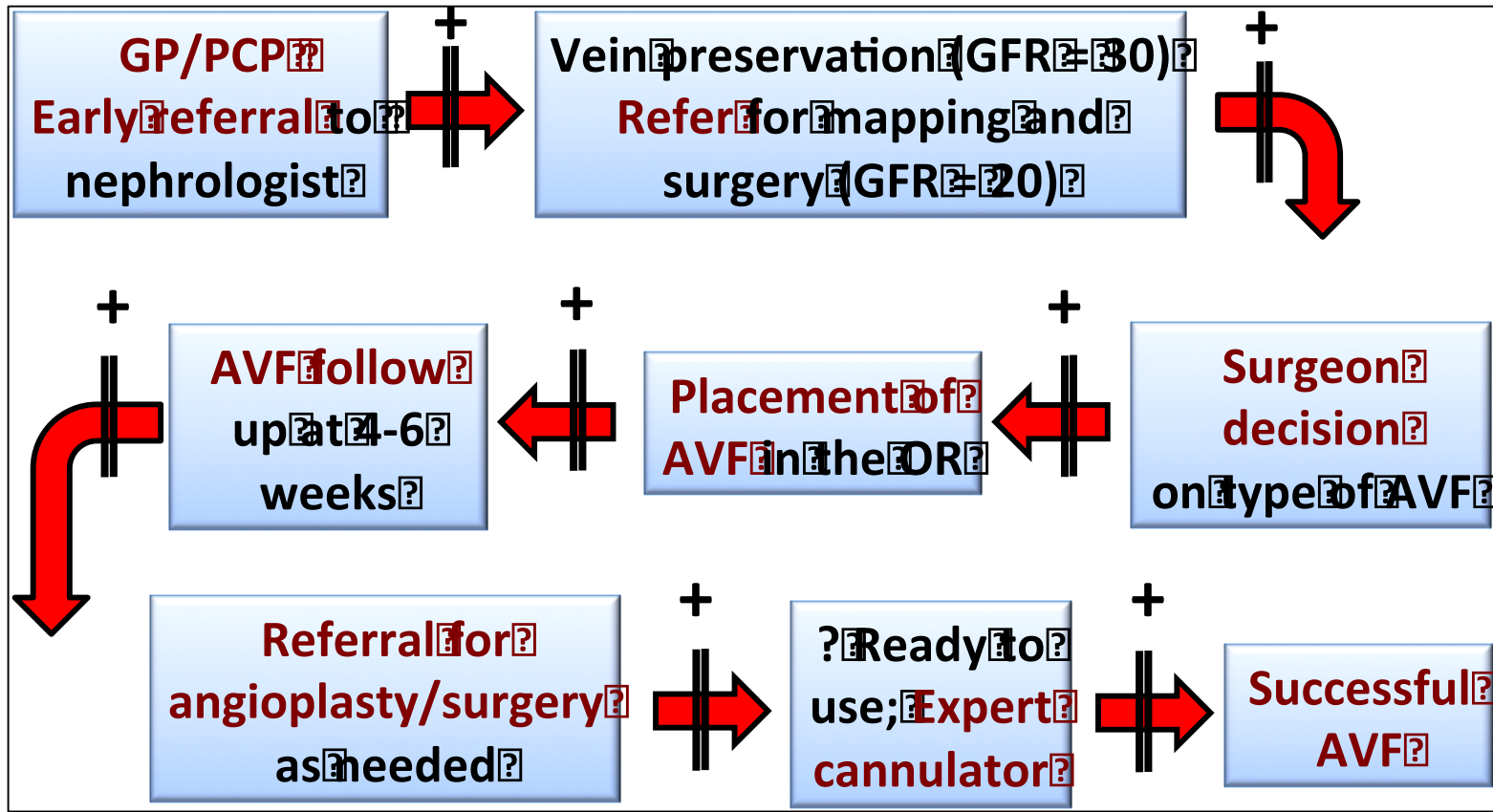
- **Catheter without infection, thrombosis or central stenosis**
- ***from* Fistula First to Catheter First and Last!!**

# Individualizing Vascular Access Care

- Get away from the one size fits all construct that we currently work under
- Stratify patients based on both biological and clinical parameters
- Offer them the sort of vascular access that is best suited to them
- Future novel therapies will allow for such an individualized approach
  - Low Risk = Standard AVF
  - Moderate Risk = AVF + drug/device or bioengineered vessel
  - High Risk = Coated catheter!



# Many of the problems in vascular access are due to Process of Care Issues

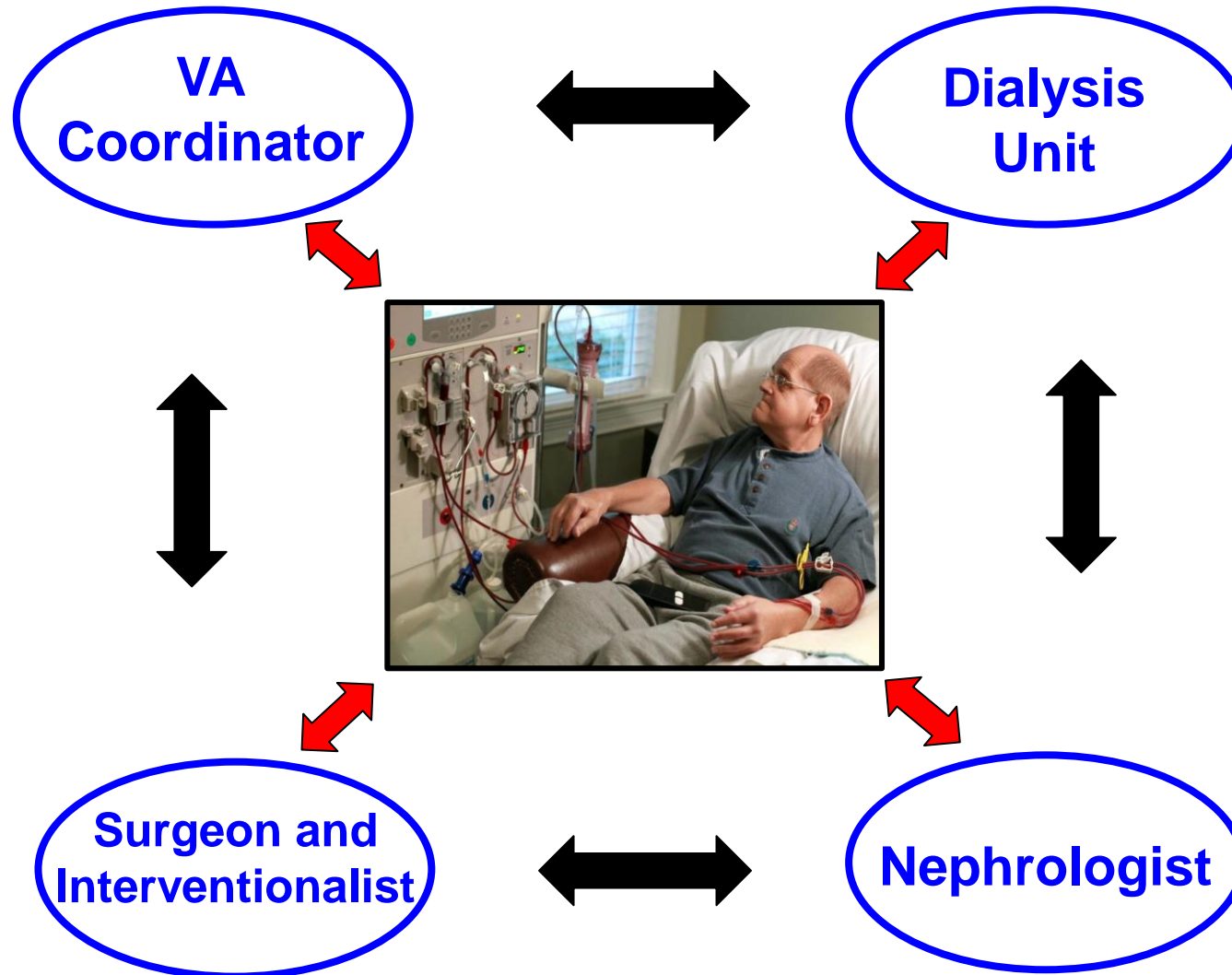


Opportunities for **LOCAL** Process of Care Innovation



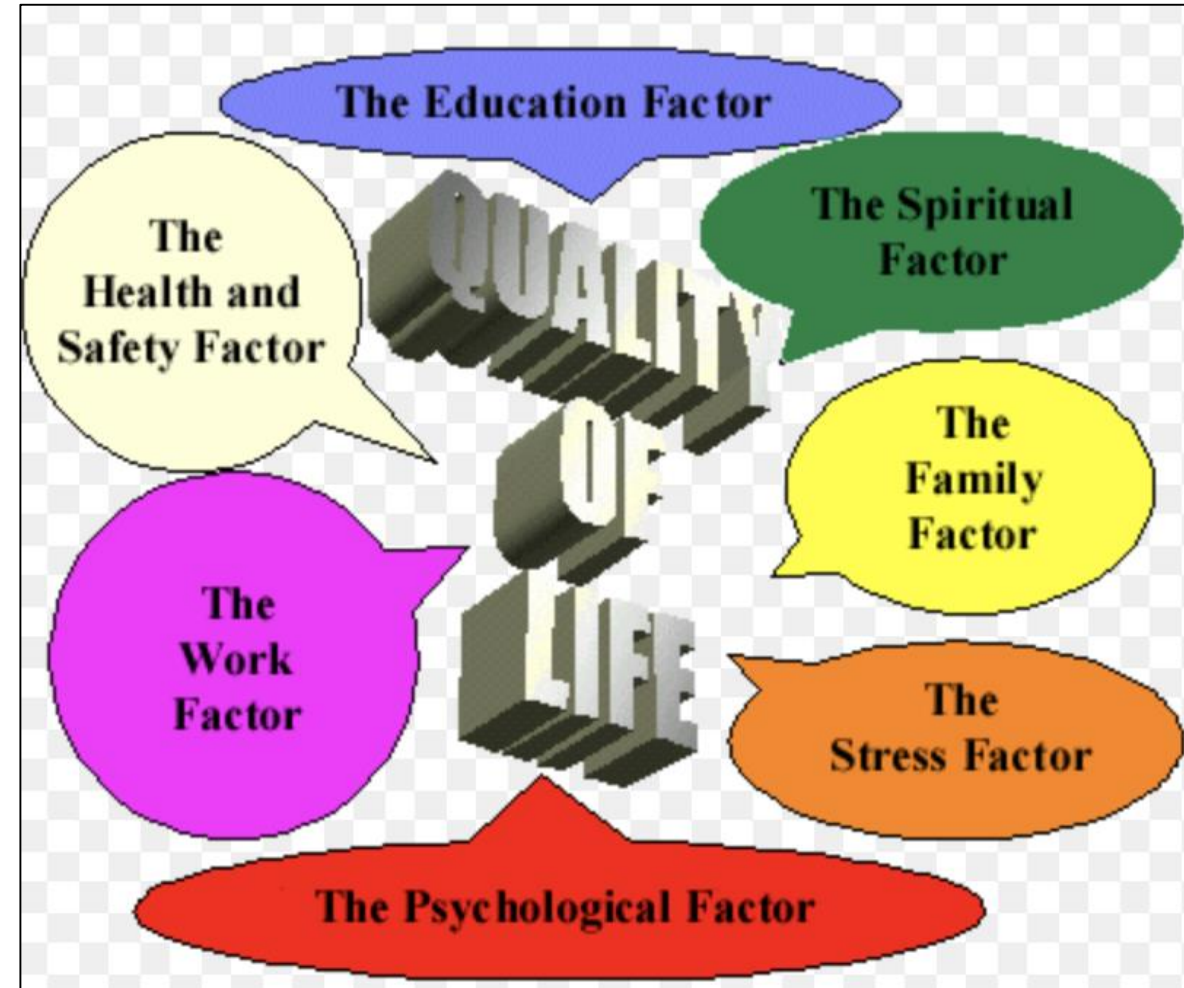
# Process of care innovation in vascular access is best done through a team approach

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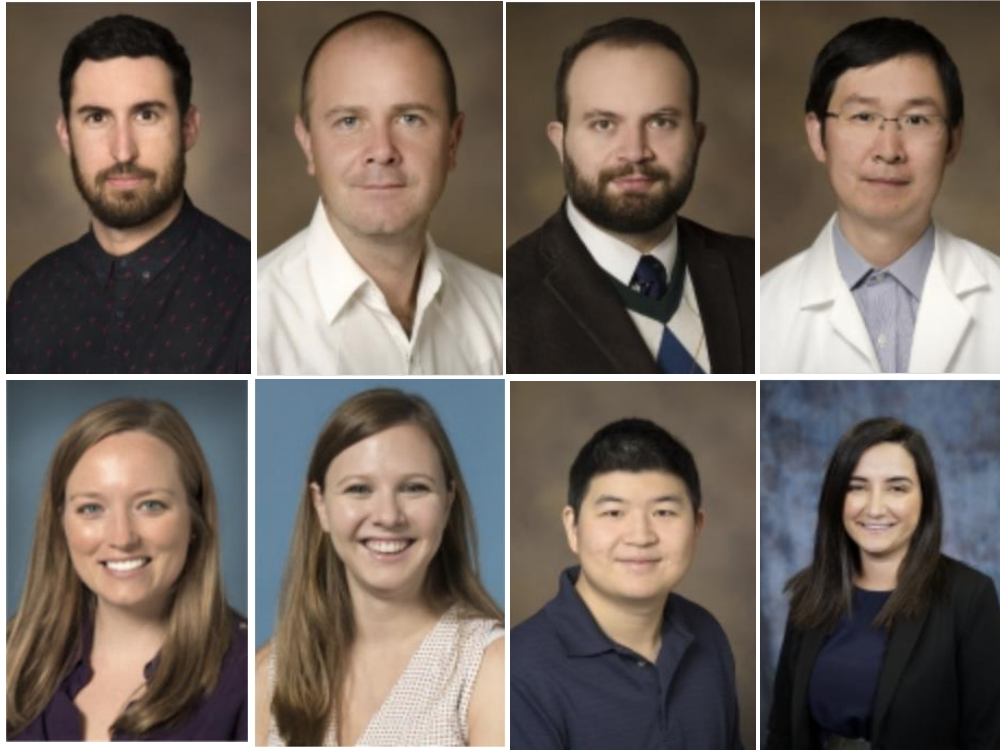


# A Personal Viewpoint

- Complex patients
- Diabetes, HTN, heart attacks and strokes, amputations, legally blind
- Social and economic issues
- We cannot fix the vast majority of these problems
- We CAN fix their vascular access by combining advances in **biology/bioengineering** with **novel technology** and **process of care** interventions
- Make a huge difference both in their survival and **quality of life**

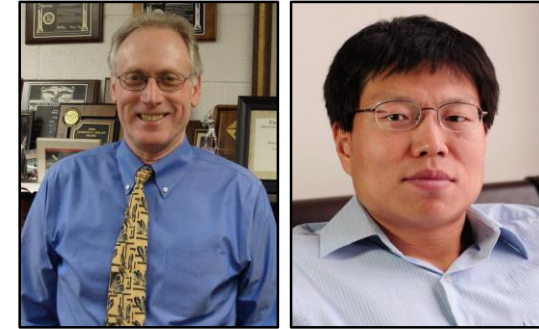


# Thank you



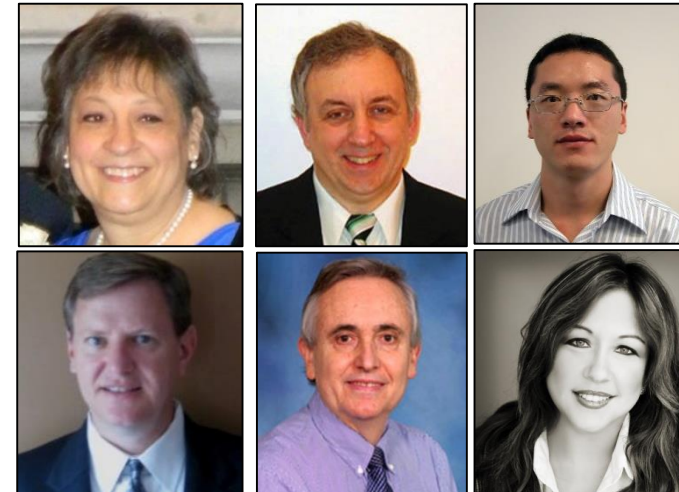
## Arizona Kidney and Vascular Center

Diego Celdran-Bonafonte	Ana Florea
Jaroslav Janda	Tom Jan
Aous Jarrouj	Ellen Santos
Lihua Wang	Lindsay Kohler
Jose Rosado	Chip Brosius



## Collaborators

Mark Meyerhof  
Yadong Wang



Begona Campos	<b>Inovasc</b>	Dan Kincaid
Mark Schulz		Vesco Shanov
John Zhang		Elsa Abruzzo

# Thank you

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# Division of Nephrology



# University of Arizona



# Synchronizing biology and technology with the clinical need or setting

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- Three times a week into a high-tech medical environment
- Get them IN; get them OUT
- Looking after their physical and psychosocial issues and vascular access
- Dialysis unit in a high-tech environment and innovation with the dialysis technology and innovation of cluster randomization in practice
- Huge opportunity to develop technologies that can be used in a positive manner during the dialysis visit itself **(for both vascular access and ESRD care)**

**Factories of Quality Care, Research and Innovation!!**

# A message for the present!!



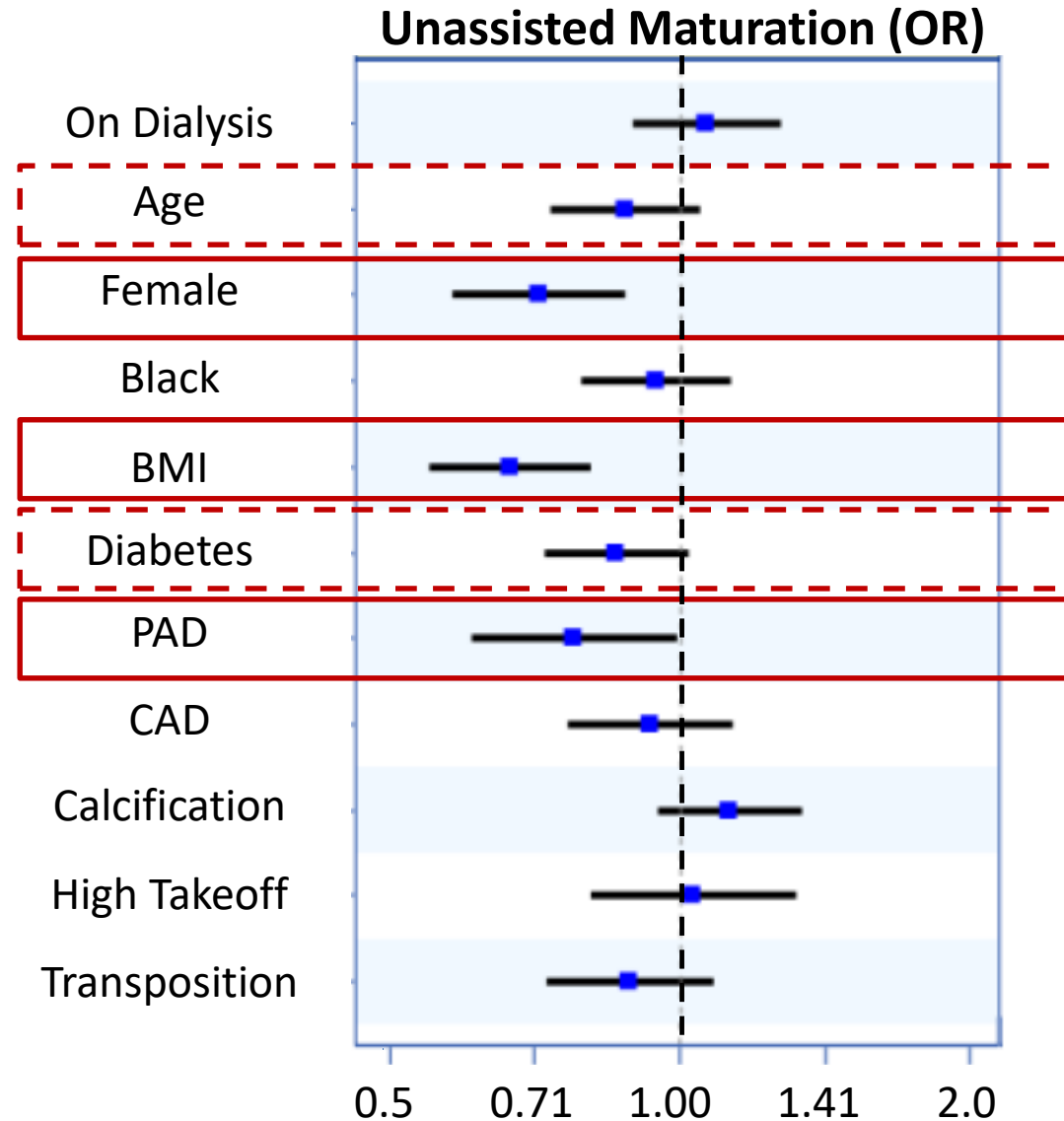
- Current modalities and therapies for dialysis vascular access are not very effective (**1 year unassisted primary primary for AVFs and AVGs < 50% at one year**)
- This results in widespread catheter use with all its attendant morbidity and mortality
- Huge unmet clinical need that needs to be addressed





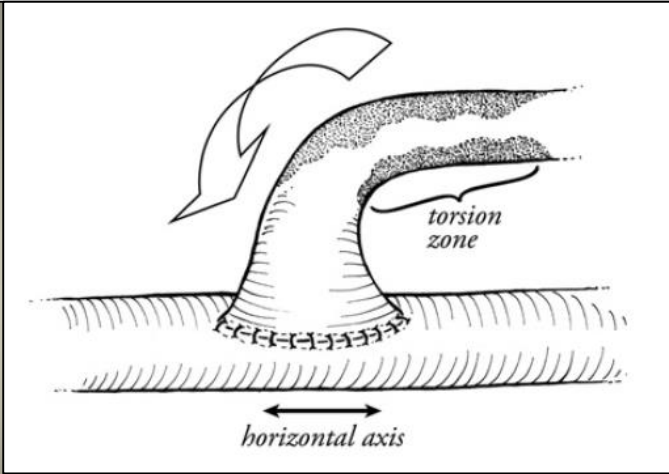
Courtesy S. Shenoy

# Clinical patient level attributes



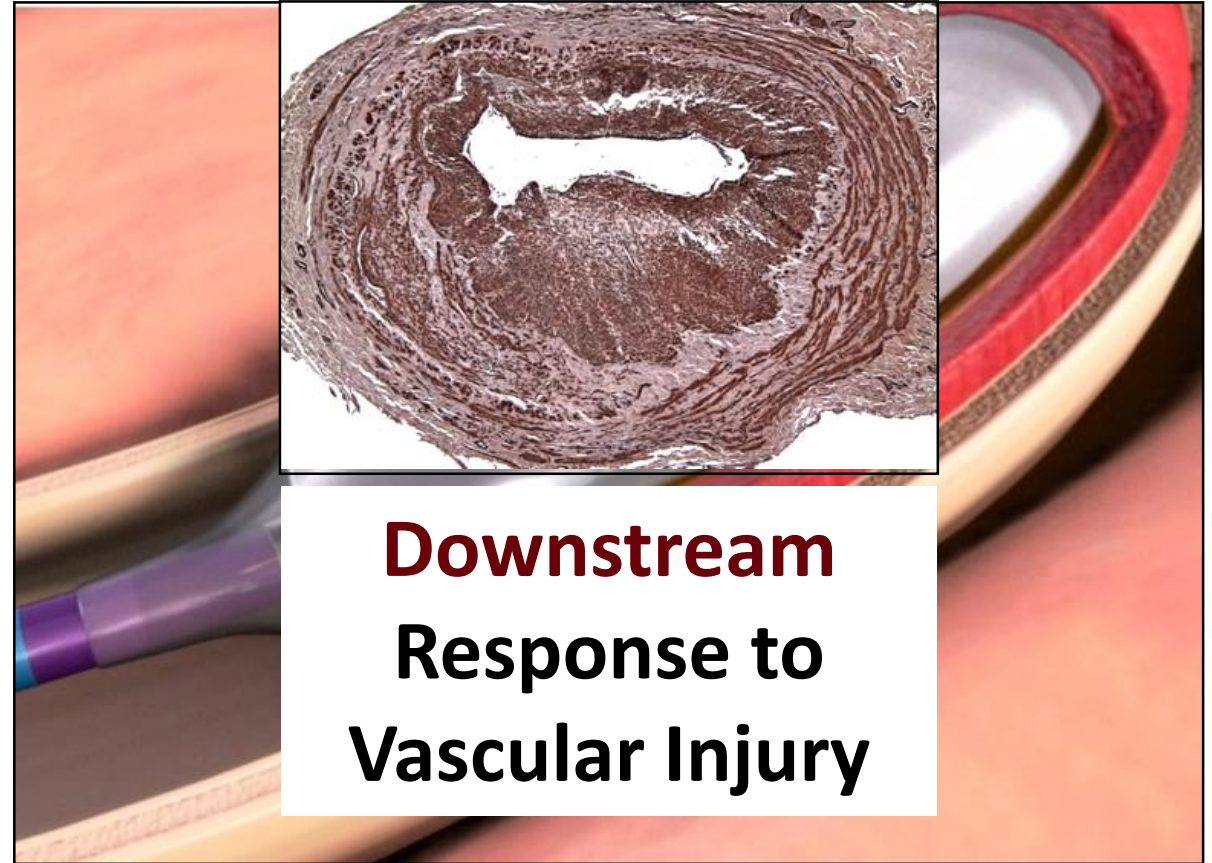


# Novel Therapies



**Upstream  
Vascular Injury**

**Endo-AVF**



**Downstream  
Response to  
Vascular Injury**

**DEB**

# Process of care innovation in vascular access is best done through a team approach

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